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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,182	06/22/2001	Keisuke Kuida	VPI/00-115 US	8856

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EXAMINER	
SHUKLA, RAM R	
ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 07/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/888,182	KUIDA ET AL.	
	Examiner	Art Unit	
	Ram R. Shukla	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's election without traverse of the invention of group I, claims 1-12 in Paper No. 12 is acknowledged.

2. Claims 13-21 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 12.

3. Claims 13-31 have been cancelled.

4. Claims 1-12 are under consideration.

5. The preliminary amendment to the specification filed 4-11-02 has been entered.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 3, 4 and 9 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a homozygous transgenic mouse embryo, whose genome comprises a mutations in the endogenous Erk5, wherein said mutation results in a non-functional Erk5 gene and wherein said transgenic mouse embryo does not produce a functional Erk5 protein and wherein said transgenic mouse embryo is characterized by a lack of vasculogenesis and angiogenesis and, does not reasonably provide enablement for any non-human mammalian embryo and other embodiments. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 2, 5-8, 10-12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one

skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

Instantly presented invention is drawn to transgenic homozygous or heterozygous non-human mammals wherein the Erk5 gene has been mutated. It is noted that the claimed invention encompasses any non-human transgenic mammal, heterozygous non-human mammals or homozygous non-human mammals and cells isolated from said mammals. However, the claimed invention is not enabled because the specification as filed fails to provide sufficient guidance for how to make and use the claimed mammals and an artisan of skill would require undue experimentation to make and use the claimed mammals as recited because the art of making any transgenic non-human mammal was unpredictable at the time of the filing of the application and is unpredictable even today as discussed below.

As the current state of the transgenic animal research stands, there are several significant limitations to the application of same methodology of making

transgenic animals to different species. Longer gestation times, reduced litter sizes, number of fertilized eggs required for micro injection and relatively low efficiency of gene integration and method of introduction of transgenes are a few examples of such limitations.

Introduction of foreign DNA into fertilized oocyte , for example by micro injection, may result in random integration of the exogenous DNA into host chromosomal DNA which in turn may have major consequences on the expression of the transgene, therefore the production of transgene in all the non-human mammals species will be highly variable and unpredictable. Even if the transgenic animals are produced, it is highly unpredictable whether transgenic animals from species other than mouse (in the present case) will be viable. In the instant case, specification discloses that even for mouse, no live birth was observed and that by there were abnormalities of placenta, embryonic yolk sac, lack of cardiovascular system and angiogenesis development by day 9.5 of embryonic development (see pages 23-25 of the specification). In view of this, it is not clear as to what would have happened in other mammalian species and whether even implantation of embryo would have occurred or up to what stage an embryo would have survived.

The steps of producing a knockout mouse that include, isolating the gene from a mouse genomic library, destroying the gene by inserting therein a selectable marker gene, introducing vectors incorporated with the destroyed gene into cultured ES cells thereby allowing homologous recombination to occur, isolating and identifying a clone in which homologous recombination has been effected, injecting the clone into a blastocyst that develops into the desired mouse. While the steps to produce knock out mouse have been well developed and used in mice, they have not been fully developed in other animals, particularly the art of gene targeting in ES cells and culture and selection of the ES cells that harbor the desired integration has been shown to be unpredictable in animals other than mice (as discussed above). Mullins and Mullins (1996) stated "However, at the present time the reliable generation of bovine ES cell lines requires the pooling of inner cell mass from several blastocysts and further efforts are required to enable the long term culture of clonal bovine ES cells. Although to date chimeric animals have been

generated from several species including the pig, in no species other than the mouse has the germline transmission of an ES cell has been successfully demonstrated " (Page 1558, para 1 in col 2).

The art of transgenesis based on ES cells is unpredictable.The art of transgenesis based on ES cells is unpredictable. Seamark (Seamark, Reprod. Fertil. Dev. 6: 653-657, 1994) states that totipotency for ES cell technology in many livestock species has not been demonstrated (see abstract on page 653). He further adds that although various studies have provided insight into what this new technology could offer to the livestock breeder, scientific and technical challenge still confront the molecular and reproductive biologist attempting to make the technology available to serve this purpose (page 653, 3rd paragraph). Moreadith and Radford (J. Mol. Med. 75:208-216, 1997) state "...indeed, the creation of mutant animals, some of which have unpredictable and subtle phenotypes, has rekindled interest in developing techniques that allow one to characterize the animals precisely."

The art of culturing and maintaining ES cells in culture is also unpredictable. Gardner and Brook (Gardner RL and Brook FA. International J. of Dev. Biol. 41:235-243, 1997) summarized the progress in the field of ES cell biology, "Remarkably little is known about mammalian embryonic stem (ES) cells despite their very widespread use in studies on gene disruption and transgenesis. As yet, it is only in the mouse that lines of ES cells which retain the ability to form gametes following reintroduction into the early conceptus have been obtained. Even in this species, most stains have so far proved refractory to the derivation of cell lines....." Additionally, gene targeting and selection of the ES cells that harbor the integration of a desired construct also has been shown to be unprdictable in animals other than mice. To prevent their differentiation, ES cells are maintained in culture in the presence of mouse derived factors that inhibit differentiation either by coculturing the cells in the presence of feeder cell lines or by adding agents to the culture as a media supplement. However, it has been suggested that such differentiation-inhibitory factors derived from mouse do not adequately prevent differentiation of stem cells in species other than the mouse. For example, rat ES cells, capable of

producing chimeras, grow best on primary rat embryonic fibroblasts as the feeder layer (see last para in col 1 on page 1558 in Mullins and Mullins, 1996) (Mullins LJ and Mullins JJ. J. Clin. Invest.97:1557-1560, 1996).

Therefore, regarding claims 3, 4 and 9 it is noted that , in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictablility of the art, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use any and all transgenic non-human homozygous mammals. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991).

Regarding, claims 1, 2, 6-8 and 10-13, it is noted that reasons for making any transgenic mammals apply to these claims as discussed for claims 3, 4 and 9. However, these claims are not enable for a mouse because the specification teaches that heterozygous mouse did not have any distinguishing phenotype and were normal (see specification page 22, lines 28 and 29). In other words, an artisan would not know how to use these mice. If the heterozygous mice are normal and do not have any abnormalities, it indicates that protein produced from one allele of the gene is sufficient for supporting normal function in the heterozygous mice and therefore cells isolated from the heterozygous mice will not have any functional abnormality and therefore, an artisan will not know how to use these cells. In other words, applicants do not teach how to use a heterozygous transgenic mouse in which ERK5 mutation does not affect any cell function. Similar to the heterozygous mice of claims 1, 2, 6-8 and the cells derived from the mice (claims 10-13), an artisan would not know how to use a cell in which only one allele of Erk5 is mutated and therefore the other allele will be producing Erk5 protein normally which would be sufficient for the cell to support normal function.

Therefore, while an artisan could make a heterozygous transgenic mouse as recited, the specification does not teach how to use such said mouse and an artisan would have required undue experimentation to use said mouse in view of the lack of any phenotype associated with ERK5 mutation.

8. Claims 1-5, 7-8 and 10-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Instantly presented invention is drawn to transgenic homozygous or heterozygous non-human mammals wherein the Erk5 gene has been mutated. It is noted that the claimed invention encompasses any non-human transgenic mammal, heterozygous non-human mammals or homozygous non-human mammals and cells isolated from said mammals.

In analyzing whether the written description requirement is met, it is first determined whether the whether a representative number of species have been described by their complete structure. Since it is not realistic to expect that the "complete structure" of any transgenic animal, or even a cell, could be described, this requirement is interpreted to be whether phenotypic consequences or other characteristics of the animals resulting from altering the genotype have been described. In the instant case, the claimed invention encompasses any homozygous or heterozygous transgenic non-human mammal whose genome has a mutation in Erk5 gene. It is noted that while the specification discloses the phenotype of a homozygous mouse embryo, there is no description of the characteristics of any other species. It is noted that while the claims drawn to heterozygous or chimeric mammals recite characteristics such characteristics are for what will be produced in a homozygous mammal and not in a heterozygous mammal. Additionally, Considering the fact that the claimed invention encompasses any transgenic mammal as well as knockout animals or non transgenic animals, and in view of the unpredictability of a phenotype(s) among different species of mammals because the art of making transgenic mammals is highly unpredictable, the description of the broad genus of mammals can not be predicted even though the phenotype of the mouse embryo is disclosed. The art teaches that phenotype of a transgenic mouse cannot be predicted. Wood (Comparative Medicine 50 (1): 12-15, 2000) noted:

"The phenotype of an animal is determined by a complex interaction of genetics and environment. It is the evaluation of the phenotype that allows us to determine the usefulness of a mutant strain as a model for biomedical research.....A specific phenotype is usually expected from genetically altered mice whether they are transgenic over-expression models or gene knockout models where a particular gene function has been modified or ablated altogether. Thus for any given genetic alteration, we often try to predict what the phenotype will be. Many times we find the predicted phenotypes or more. It is, however, common to hear that surprisingly a given model has "no phenotype"."

This clearly indicates that the phenotype of a transgenic mouse or rat or any animal cannot be predicted. Therefore, the specification does not describe the phenotype of a representative number of species of the genus.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. In case of a knockout animal, it is not possible to adequately describe the claimed animals because the effects of inactivating a gene cannot be predicted, particularly when a gene product may be interacting with the proteins of a family of proteins. For example, Korach et al (US Patent No. 5,650,550, 7-22-97) produced a knockout mice lacking a functional estrogen receptor. One skilled in the art would not have predicted that such an animal would even be viable (see col 9, lines 22-39), much less have been able to predict the resulting phenotype. In the instant application, it is emphasized that no viable mouse birth was obtained and therefore one would not be able to predict the result of inactivating Erk5 gene in the transgenic mammals encompassed by the invention. With the limited information disclosed in the specification, an artisan would have not been able to predict whether all these animals would have had same or different phenotypes compared to the knockout mice or transgenic mice.

Therefore, the limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the huge genera recited in the claims at the time the application was filed. Thus it

is concluded that the written description requirement is not satisfied for the claimed genera.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1, 2, 6-12 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 6 are vague and indefinite because the limitation "wherein a.....embryos" does not limit the claims since the claims are drawn to a heterozygous mammal which cannot have this limitation. It is not clear as to how this limitations limits the scope of the claimed mammal.

Claims 2 and 7-12 are indefinite because they are dependent on claims 1 and 6.

11. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ram R. Shukla whose telephone number is (703) 305-1677. The examiner can normally be reached on Monday through Friday from 7:30 am to 4:00 p.m. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for this Group is (703) 308-4242. The after-final fax number is (703) 87209307. Any inquiry of a general nature, formal matters or relating to the status of this application or proceeding should be directed to the William Phillips whose telephone number is (703) 305-3413.

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER

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Art Unit 1632